REMARKS

Claim 48 is canceled without prejudice. Claims 33, 35, 37, 38, 39, 40, 47, 58, 59, 60, 62, 63 and 64 are amended to address the Office's assertion that the relationship between the parent cutinase and the variant cutinase is unclear.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Rejection of Claim 33 under 35 U.S.C. 112

The Office indicates in the Advisory Action of March 30, 2004 that claim 33 would be rejected under 35 U.S.C. 112 because the relationship between the parent cutinase and SEQ ID NO:1 is unclear.

Applicants respectfully submit that this rejection is rendered moot by the amendments. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims ? under 35 U.S.C. 112

Claim 48 is rejected under 35 U.S.C. 112, as allegedly introducing new matter. The Office states that the specification does not support the variant E6Q+A14P+N15T+E47K+R51P+A130V+E179Q.

Applicants respectfully disagree. Nevertheless, in order to expedite prosecution, claim 48 has been canceled. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 33-48, 53 and 58-65 under 35 U.S.C. 112

Claims 33-48, 53 and 58-65 are rejected under 35 U.S.C. 112, as allegedly lacking enablement. In the Advisory Action, the Office states that Applicants arguments were not persuasive. In particular, the Office states:

> [W]hile methods to produce variants of known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as clamed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of the great number of variants that have the activity or an activity of an additional claimed property (claims 43-45). Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly

> constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

This rejection is respectfully traversed. "A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369. It is well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988).

The Patent Office concludes that the specification does not provide sufficient guidance to practice the claimed invention by introducing the claimed alterations into cutinases which possess above 80% homology to SEQ ID NO:1. Applicants respectfully disagree.

Foremost, the claimed cutinase variants are very structurally similar in that they possess above 80% homology to SEQ ID NO:1. As discussed in Applicants' prior response, based on this high degree of structural similarity, the artisan would reasonably expect that the modifications recited in the claims and exemplified in the specification would be applicable to this genus of homologous structures.

The specification also provides an extensive disclosure of techniques which are well-known in the art for obtaining homologous structures and indeed it was routine for persons of ordinary skill in the art at the time of the invention to prepare cutinase variants which possess above 80% homology to SEQ ID NO:1. See, e.g., the specification at page 2, lines 5-6, and the disclosure beginning at page 7 under the heading "Methods for Preparing Cutinase Variants." The specification also provides working examples exemplifying the ability of an artisan to produce and screen cutinase variants which possess above 80% homology to SEQ ID NO:1. See Examples 1-5.

In the Advisory Action, the Patent Office concedes that it was routine for the skilled artisan to produce cutinase variants having above 80% homology to SEQ ID NO:1, however,

the Office indicates that the lack of enablement is based on the extent of selection or screening required to identify such variants, and that Applicants have not provided appropriate guidance. The Patent Office's conclusion may have been true many years ago, however, such conclusion was certainly not the case as of the effective filing date of this application. As of October 2000, persons of ordinary skill in the art were unquestionably able to routinely produce and screen in a short period of time thousands to hundreds of thousands of mutants of a known sequence through mutagenesis and other techniques. Such technology available to the artisan at the time of the invention included random mutagenesis protocols described in WO 95/22615. Moreover, the gene shuffling protocols of Stemmer (see, e.g., U.S. Patent No. 6,365,408) and other gene diversity protocols, also available to the artisan at the time of the invention, permit an artisan to rapidly generate virtually all of the possible variants of a sequence, and certainly, cutinases variants having 80% homology to SEQ ID NO:1.

The Office alleges that because the specification does not have appropriate guidance for producing cutinase variants having 80% homology to SEQ ID NO:1, that one of ordinary skill in the art would be reduced to producing and testing all of the virtually infinite possibilities. First, no where do the claims require (nor is it necessary for enablement) that the artisan "produce and screen all of the virtually infinite possibilities." Applicants are not suggesting that one skilled in the art go out and make all of the possible cutinase variants falling within the claims. Rather, Applicants' specification and claims teach that the specification enables one skilled in the art to make and use the claimed sequences and clearly define the metes and bounds of the claimed invention.

However, although the claims do not require "producing and testing all of the virtually infinite possibilities" of sequences which are at least 80% homology to SEQ ID NO:1, the artisan was even able to carry this task out. Indeed, as previously discussed, as of the time of the claimed invention, the technology permitted the skilled artisan produce and screen in a short period of time thousands to hundreds of thousands of mutants of a known sequence through random mutagenesis protocols (see, e.g., WO 95/22615). Moreover, using the gene shuffling protocols of Stemmer (see, e.g., U.S. Patent No. 6,365,408) and other gene diversity protocols, an artisan was able to rapidly generate "virtually infinite possibilities of sequences". Thus, the Patent Office has assumed a fact as the basis for the enablement rejection which is absolutely incorrect.

The Patent Office states that the specification does not provide sufficient guidance for identifying suitable cutinase variants. This is also not correct. Again, as previously discussed

and as acknowledged by the Patent Office, an artisan was readily able to create cutinase variants which are more than 80% homologous to SEQ ID NO:1 and contain the claimed mutations. The only other tasks required to enable the claimed invention is for the artisan to screen for whether the variant has cutinase activity (all claims), screen for whether the variant has hydrolytic activity towards terephthalic acid esters (claim 43), screen for whether the variant has hydrolytic activity towards has hydrolytic activity towards cyclic tri(ethylene terephthalate) and/or Terephthalic acid bis(2-hydroxyethyl)ester dibenzoate (claim 44) or screen for whether the variant has a denaturation temperature which is at least 5°C higher than the parent cutinase at pH 8.5 (claim 45). The Patent Office cannot legitimately conclude that such tasks are not well within the skill of the artisan. The evidence in Applicants' examples also rebuts this conclusion.

The conclusion reached by Patent Office that infinite screening and selection creates enablement problems can only be obtained by improperly associating undue experimentation with the time required for a task. However, the Federal Circuit long ago put an end to such conclusions, as the fact that a task may take time does not mean that the task involves undue experimentation. See *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, as of the time of the claimed invention, the time required for producing and screening massive variant libraries was insignificant, based on among other things, the advancement in computerized and robotic screening technology.

Thus, the conclusion of lack of enablement has not given consideration to the skill of the artisan practicing the claimed invention. For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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Jason I. Garbell, Reg. No. 44,116
Novozymes North America, Inc.
500 Fifth Avenue, Suite 1600
New York, NY 10110
(212)840-0097